nosis. Coproporphyrin-III and a very small amount of coproporphyrin-I were also found. Fig. 2 represents the day-to-day excretion of uroporphyrin and of coproporphyrin from the 19th to the 23rd week after admission. The daily variations in pulse rate are also charted. An increase in porphyrin excretion was associated with a rise in pulse rate, though the correspondence was not exact.

Conclusion

The administration of sulphonamides or of barbiturates may precipitate an attack (Mason *et al.*, 1933; Waldenström, 1939; Nesbitt and Watkins, 1942). Phenobarbitone, 1 gr. twice daily, was given for periods of several weeks during the third and fourth attacks, but there was no evidence that the drug affected their course adversely. The onset of the sixth relapse cannot be attributed to the administration of sulphathiazole, as the patient had then been losing weight for about four weeks—a sign, in his case, of pending relapse. A noteworthy feature of the disease is the degree of restoration of function of the paralysed muscles, which in this patient appeared nearly complete.

Summary

A patient complaining of attacks of abdominal pain, constipation, and fits was found to be excreting uroporphyrin-III in his urine and to be suffering from acute porphyria. A marked decrease in body weight preceded the onset of symptoms.

In the course of three years he experienced six relapses, in each of which the symptomatology varied. Recovery now appears to be complete although porphyrinuria persists.

In one attack the daily variation in porphyrin excretion was determined.

The clinical features of the disease and methods by which the diagnosis may be confirmed in the laboratory are described.

We wish to thank Dr. Geoffrey Evans for permission to publish this case.

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SIMMONDS'S DISEASE DUE TO POST-PARTUM NECROSIS OF THE ANTERIOR PITUITARY: CARCINOMA OF STOMACH

BY

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Although the papers by Sheehan (1938, 1939, 1940) and Sheehan and Murdoch (1938, 1939) have clarified knowledge as to the causation of Simmonds's disease and stimulated interest in this condition, descriptions of cases due to necrosis of the anterior pituitary lobe resulting from post-partum collapse are still rarely seen in the clinical journals. The following case may therefore be of interest. It is reported alone, although other presumptive cases have been seen in this department during the past few years, including that of a woman who had amenorrhoea dating from the birth of her last child when she was 30, and who died, aged 39, of carcinoma of the bladder, with an extensive neoplastic spread in the pelvis. Post-mortem examination revealed splanchnomicria and (both to the naked eye and in serial sections) the typical atrophy in the anterior pituitary. Owing to her general condition, however, few investigations had been done during life.

Case Report

Mrs. W., aged 59, was referred for investigation on Feb. 23, 1943, by Dr. F. M. Rose, of Preston. She gave a history of progressive tiredness and loss of 1 st. in weight over the past year, and anorexia and numbness of the fingers since an attack of influenza in 1942. She had mentioned epigastric pain to her doctor, but told me that there had been no pain, vomiting, epistaxis, or dysphagia. She had had four pregnancies; her son was aged 37, the middle two children had died at 11 months and 2 years old, and her daughter was 27. The first three confinements were uncomplicated, but at the birth of the last child, when the patient was 32, there was severe haemorrhage and she was in bed seven weeks or more from weakness. She menstruated 5 months later, and again, for the last time, four months after that. After the delivery she did not lactate, and the breasts, from being large, became very small. Loss of hair was soon noticed (especially axillary and pubic), and she gained 1½ st. in weight. A year passed before she regained her strength. Sensitivity to cold developed, becoming more pronounced during the last year. No change in sex feelings could be recalled. The patient's daughter-in-law said that she had been pale for 15 years or more, but the pallor had become more grey over the past year, and the cheeks were sunken. No psychological changes had been noted, such as peevishness, unkindness, absentmindedness, faints, fugues, or attacks of coma.

Examination.—Height, 5 ft. 1 in.; weight, 6 st. 11 lb. The pallor and wasting gave the clinical picture of cachexia; face wrinkled, cheeks sunken, no glossitis; axillary and pubic hair absent; scalp hair thin; eyebrows very thin; breasts flat and atrophic; soft quick pulse, with occasional dropped beats (B.P. 100/60); oedema of lower legs; nothing abnormal felt in abdomen. Physical examination otherwise negative.

Blood Counts, 1943

	Hb Haldane	R.B.C. (mills.)	Anisocytosis	M.C.V. (c.μ)	Mean Diam.	Leucocytes	
						Total	Neut.
Feb. 23	100	4·4	Slight	86	7·7μ	6,400	2,900
Mar. 17	95	4·2	,,	—	—	8,400	4,500
April 2	74	3·7	,,	—	7·8μ	—	—

Blood Chemistry

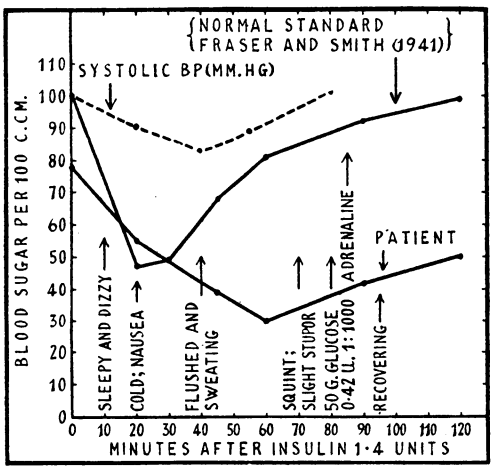
	Feb. 23	Mar. 12	Normals
Bilirubin (mg./100 c.cm.)	0·7	—	—
Calcium ,,	—	8·5	9– 11
Chlorides ,,	568	570	560–620
Cholesterol ,,	125	132	120–230
Phosphate ,,	—	4·2	3– 4·5
Phosphatase ,,	—	15	3– 13
Potassium ,,	25	24	18– 21
Protein (g./100 c.cm.)	—	7·1	6– 8
Sugar (true) fasting (mg./100 c.cm.)	65	—	65–100
Glucose-tolerance test (50 g.)	80–150–70	—	—
Urea (mg./100 c.cm.)	25	—	—
Sodium ,,	297	—	300–325

Progress.—Feb. 23: Urine normal. Feb. 25: B.M.R., -9%. Fractional test meal: Histamine-fast achlorhydria without evidence of stagnation or organic lesion. March 9: Glucose-tolerance test—normal curve; electrocardiograph, "T_2 inverted" (Dr. Harold Isaacson). March 12: B.M.R., −37%. March 24: Insulin sensitivity test (Fraser and Smith, 1941). As there were clinical grounds for suspecting pituitary insufficiency, one-third of the standard dose of insulin was used—i.e., 0.1 unit per 3 kg. of body weight. After 1.4 units of insulin had been given intravenously the blood sugar fell from fasting level of 78 mg. per 100 c.cm. to 38 mg. per 100 c.cm. in 45 minutes and 30 mg. per 100 c.cm. in 60 minutes. In the healthy subject symptoms of hypoglycaemia should not persist after this one-hour point. As the patient then showed slight clouding of consciousness and a slight squint, the test was cut short by 50 g. of glucose orally, and an intramuscular injection of 0.42 c.cm. of 1:1000 adrenaline. The lowest figure for the systolic blood pressure was 82 mm. Hg 40 minutes after the insulin. She was admitted to hospital for a rest and was discharged two days later feeling no ill effects.

[The following explanation of the insulin sensitivity test is quoted from Fraser and Smith (1941): "The rate of the initial fall in the blood sugar differentiates normal or increased insulin sensitivity from insulin resistance; and the speed of the subsequent return to the fasting level will indicate any tendency to persistence of hypoglycaemia—that is, a delay in return will indicate 'hypoglycaemia unresponsiveness,' which may be found mainly in hyperinsulinism, hypo-adrenocortinism, or panhypopituitarism. Thus the characteristic result of this test in panhypopituitarism is a normal rate of fall associated with an abnormally slow return to the fasting level, or 'hypoglycaemia unresponsiveness'."]

The accompanying Graph shows the slow and prolonged fall of the patient's blood sugar and the typical delayed rise. Fraser and Smith's "index of hypoglycaemia unresponsiveness" is 320 (normal 550 ± 70). The result of this test, therefore, was further evidence for the presence of a lesion in the anterior hypophysis.

May 1.—Urinary 17-ketosteroid assay (Fraser and Smith, 1941): result—zero figure in 24-hour sample of urine, using Callow and others' (1939) modification of the method of Dingemanse, Borchardt, and Laqueur (normal value for women, 1.7 to 12.6 mg. in 24 hours). After attending for a blood count on April 2, Mrs. W. was unable



to report here again. She received no specific treatment and slowly weakened. She died on Oct. 6, 1943, of cachexia and heart failure.

Necropsy (Oct. 6, 1943).—Dryness and desquamation of the skin, oedema of legs; moderate amount of clear fluid in pleural and pericardial sacs; very small thyroid (6.5 g.); thymus not seen; small heart (150 g.); fibrosis at apex of left lung (right 380 g., left 240 g.); thin intestinal wall; small liver (650 g.); spleen, 65 g.; cancerous ulcer in pyloric antrum of stomach 1 in. across and puckering the peritoneum; no metastases or neoplastic glands; adrenals atrophic—combined weight 5 g., cortices very thin, medullae not obvious; kidneys 85 and 100 g., capsules strip smoothly, fine cortical cysts, cortices slightly narrow; tiny uterus (25 g.) and ovaries (3 g. the pair). The base of the brain was hardened *in situ* by formalin in the skull overnight. The pituitary, when removed still attached to the brain, appeared as a collapsed empty shell.

Histology.—Thyroid: Increase of fibrosis. Adrenals: Partial atrophy. Uterus: Atrophy of endometrium and myometrium. Ovaries: Atrophy. Left lung apex: Fibrosis; anthracosis. Liver: Fat ++ ; variable size of cells and nuclei. Kidneys: Exudate in glomerular spaces; some tubular debris. Spleen: Follicular fibrosis. Pyloric ulcer: Adenocarcinoma. The pituitary was not sectioned; the base of the brain, with attached hypophysis, was given to the Royal College of Surgeons.

Summary

A case of Simmonds's disease is described in a woman aged 59, due to necrosis of the anterior pituitary dating from a confinement 27 years before.

Attention to the obstetrical history makes the presumptive diagnosis simple in this condition.

Among other clinical pathological tests the results of the insulin sensitivity test and the urine 17-ketosteroid assay added weight to the diagnosis.

Necropsy revealed a general splanchnomicria as expected, but also an "early" pyloric carcinoma which was not expected. Was this a coincidence, or was it another result of the pituitary lesion?

I am grateful to Drs. F. M. Rose and F. B. Smith for their co-operation and permission to publish, and to Mr. G. E. Delory, M.Sc., for help with the biochemical tests. I wish also to thank Lieut.-Col. H. L. Sheehan for much interesting advice and correspondence.

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J. D. Durance (*J. R.A.M.C.*, 1945, **84**, 280) maintains that, though there are other causes of subconjunctival petechiae, it is safe to treat as positive all cases of pyrexia or mental disturbance exhibiting these signs on the first day of the disease during an outbreak of cerebrospinal fever, and begin chemotherapy immediately. The absence of subconjunctival petechiae is a good prognostic sign.

HAEMOLYTIC DISEASE AND CONGENITAL SYPHILIS IN SIBLINGS

THE ROLE OF THE Rh FACTOR

BY

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It has been alleged that congenital syphilis may give rise to a clinical picture identical with erythroblastosis (Holt and McIntosh, 1933). A history of neonatal jaundice, foetal dropsy, or intra-uterine death in successive pregnancies has been regarded in the past as confirming the diagnosis of syphilis. On this supposition, even in the absence of serological and histological evidence of the disease, women with such unfortunate obstetric histories have been subjected to prolonged courses of antisyphilitic treatment. Syphilis and erythroblastosis foetalis (or haemolytic disease of the newborn, as it is now called—Parsons, 1943) resemble each other in that each may cause the repetition of obstetric disasters; but the obstetric histories differ characteristically in the two conditions, the earlier children usually being spared in haemolytic disease but dying in syphilis. Levine *et al.* (1941) discovered that the chief cause of haemolytic disease lies in iso-immunization of the mother to the blood-group factor Rh, present in the foetal cells and absent from her own. Tests for the Rh factor are thus of value in differential diagnosis, and provide a criterion by which the importance of syphilis, umbilical sepsis, or other alleged cause of erythroblastaemia may be assessed. Since the discovery of the possible results of blood-group incompatibility between mother and foetus the formerly alleged causes of erythroblastosis can no longer be accepted until it has been clearly proved that there is no evidence of, or basis for, iso-immunization. There does not appear to be any published example of erythroblastosis in a newborn syphilitic infant in which a concurrent Rh incompatibility between the mother and child has been excluded. Henderson and Macgregor (1943) reported a case of hydrops foetalis (haemolytic disease Type I) in the child of a syphilitic primigravida with anti-Rh agglutinin in her serum and with unequivocal histological evidence of erythroblastosis in the foetal tissues. This case supports the new concept that the foetal condition was attributable to the Rh incompatibility rather than to the syphilis.

I have recently observed a family in which haemolytic disease and congenital syphilis have appeared in siblings. This family illustrates well the value of tests for the Rh factor in confirming the diagnosis of haemolytic disease in the presence of maternal syphilis.

Case Notes

Mrs. C., aged 34. Group A_1 Rh-negative (rr). Husband overseas. Obstetric history: (1) 1935: female, premature, alive, Group A_1 Rh-positive. (2) 1939: male, full-time, died of icterus gravis neonatorum (haemolytic disease Type II). (3) 1941: six-months miscarriage. (4) Female, full-time, alive, Group O Rh-negative.

In 1939 the patient gave birth to a full-time male child who became jaundiced some hours after birth and died two days later. This infant was put to the breast, and on account of jaundice and petechiae in the skin he was given an intramuscular injection of 18 c.cm. of maternal blood. During this pregnancy the diagnosis of maternal syphilis had been made, and the mother continued to receive antisyphilitic treatment more or less regularly from that time until early in the fourth pregnancy. Post-mortem examination of the second infant revealed widespread erythroblastosis of the organs with abundant extramedullary haemopoiesis, the appearances being characteristic of haemolytic disease Type II. Histological evidence of syphilis was entirely lacking in all the organs and tissues.

In 1942, in the course of a study on haemolytic disease of the newborn, this patient's blood was first examined for the Rh factor and found to be Rh-negative. It was then disclosed that she had had a miscarriage about 20 months previously, and, in spite of the lapse of time since her last pregnancy, powerful anti-Rh agglutinins were present in her serum (titre 1/128).

In 1944, during the fourth pregnancy, the maternal serum was tested repeatedly from the fourth month onwards, from which time the patient remained under observation in hospital on account of her cardiac condition. The Wassermann reaction was positive, and the serum contained anti-Rh agglutinin type anti-Rh_1 (i.e., rho and rho_1) throughout the remainder of the pregnancy (titre 1/128).